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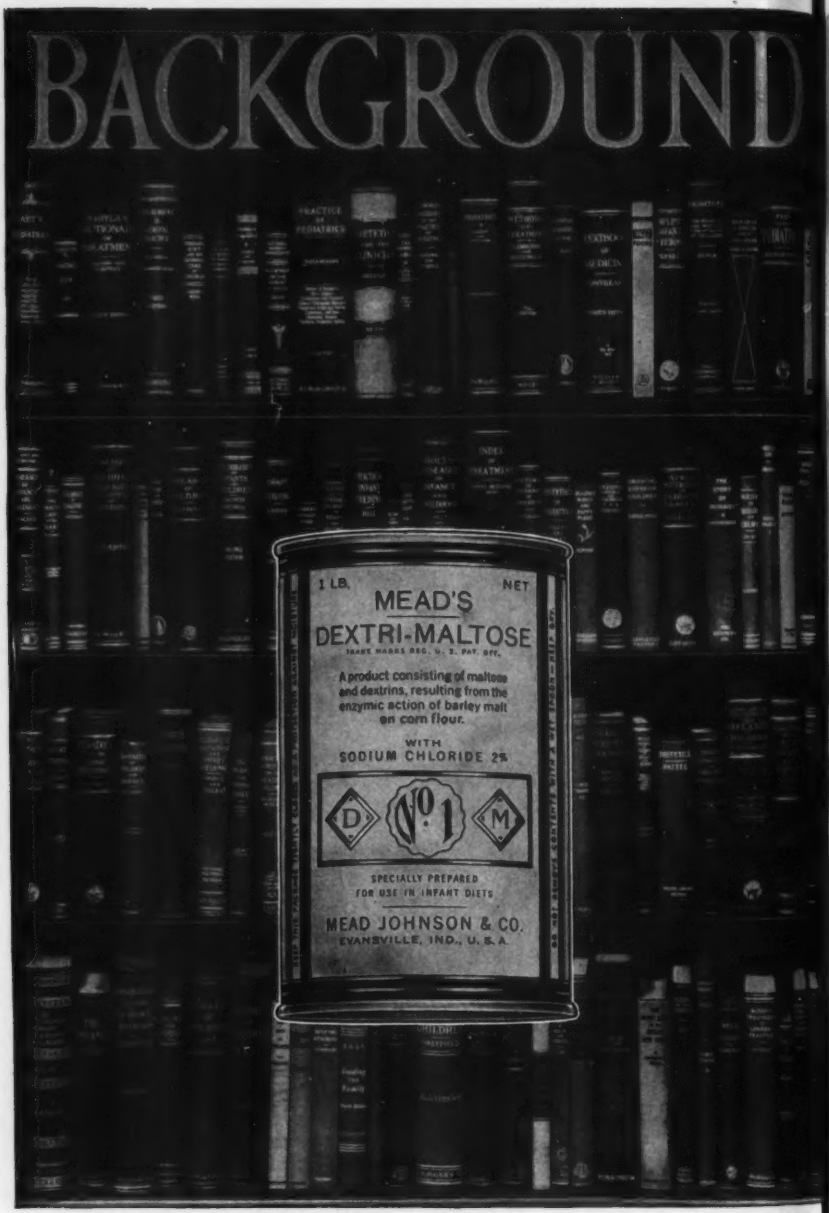

THE use of cow's milk, water and carbohydrate mixtures represents the one system of infant feeding that consistently, for over three decades has received universal pediatric recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of authoritative clinical experience as Mead's Dextri-Maltose.

SPECIAL REPORT

NEUROBLASTOMA

Case Report and Discussion

D. Joseph Judge, M.D.
Bennett Olshaker, M.D.
Paul Kaufman, M.D.
Howard Kuder, M.D.
Edwin Vaden, M.D.

Dr. Judge:

One of the commonest abdominal tumors in children and one of the most malignant is the neuroblastoma of the adrenal gland. Steiner[1] reported 16 neuroblastomas (including eye) in a group of 123 malignant tumors in a representative report, which covered a 30 year period up to 1946, of the Department of Surgical Pathology at the Chicago Children's Hospital. Ladd and Gross,[2] during one period reviewed, considered Wilms' tumor less common than neuroblastoma.

The past few years have brought forth some enlightenment as to the clinical picture, diagnosis and suggested forms of treatment in this disease, but the gap in knowledge is still wide. Few pediatricians see enough cases during their lifetime to make adequate observations on which final conclusions can be drawn or great experience can be derived. It has been our lot to observe the unusual occurrence of four neuroblastomas of the adrenal gland within an 8 week period. This is 40 per cent as many cases as observed from 1932 to 1947.

Case Report No. 146

Dr. B. Olshaker: D. H. 48–10028

D. H., a 2 year old white male, on the service of Dr. F. Zinzi was first admitted to Children's Hospital on August 29, 1948. He had been well until just before his first admission to the hospital when he began to have recurrent fever, intermittent vomiting, and frequent frontal headaches. Shortly after the onset a clinical similarity to poliomyelitis with stiffness of the left arm and neck, and a limp of the right leg developed. During the succeeding week swelling of the right eye occurred on two occasions and was apparently relieved by penicillin. The neck stiffness disappeared in one week but weakness of both lower extremities persisted until admission. Three weeks before admission hemorrhages under the skin of his left upper lid, nose, right shoulder, back, and arms were noted, "dime to

quarter" in size, which subsequently faded. An examination, chest x-ray and urinalysis two weeks prior to admission to Children's Hospital were reported as negative although red urine had been noted. An anemia was treated with iron preparations. In August hospitalization was advised by a physician.

The dietary and development history was essentially negative.

On admission physical examination revealed a well developed and well nourished, moderately pale two year old white male who was not in acute distress. Temperature was 104°F., pulse 140 and respirations 16. There was a 1 to 2 plus generalized lymphadenopathy but otherwise the examination was negative. Hemogram on admission showed 7.5 grams of hemoglobin, 2,900,000 erythrocytes, and 14,000 leucocytes with a 42 per cent polymorphonuclears and 54 per cent lymphocytes. The bleeding time was 1½ minutes and coagulation time was 3½ minutes. There were 300,000 platelets. Urinalysis was negative. Agglutination tests with febrile antigens were negative.

A diagnosis of nutritional anemia was made and the patient was given two transfusions of 200 cc. of whole blood and responded well. Six days after admission the hemogram was normal while the temperature had returned to normal base line on the second hospital day. The child was discharged on his 6th hospital day.

He was readmitted to the hospital on September 13th, 10 days after his discharge when irritability, anorexia, malaise, vomiting and generalized abdominal pain developed.

Physical examination at the second admission revealed a proptosis of the right eye with a fixed pupil, otherwise there had been no change since the previous admission. Hemogram showed 9 grams hemoglobin, 3,200,000 erythrocytes and 6,100 leucocytes with 48 per cent polymorphonuclear cells. Urinalysis was negative. Stool examination for occult blood and urine culture were negative.

X-ray of the chest and upper abdomen were negative. An x-ray of the skull showed the anterior fontanelle to be incompletely closed. An intravenous pyelogram disclosed a marked displacement and rotation of the right kidney away from the midline with compression of the ureter on that side. Calcification was seen in the region of the right adrenal gland. The sacrum, pelvis, and proximal portions of the femorae showed diffuse areas of decreased density with irregular areas of condensation of the heads of the femorae and some periosteal reaction along the shafts. The lower ribs and probably the lumbar vertebrae showed similar changes. X-rays of the long bones of the upper and lower extremities revealed some malignant infiltration throughout the humeri, a periosteal reaction, and early areas of rarefaction in the distal head of the tibia. The roentgenographic and clinical diagnosis of neuróblastoma of the adrenal was made.

After a blood transfusion the child was discharged for irradiation therapy on an out-patient basis.

Three weeks later the boy was admitted for the final time. During the interim he had received 2472 r of radiation. Roentgenographic evidence of skull and shoulder girdle metastasis had been found. Physical examination disclosed a malnourished and chronically ill child. There was a generalized shotty lymphadenopathy. The head was markedly enlarged and measured 55 cm., an increase of 2 cm., in ten days, and the scalp veins dilated markedly. The anterior fontanelle and the saggital suture were open. Both eyes appeared proptosed with the left slightly more than the right. The pupils were dilated and did not react to light. There were ecchymotic areas in both eyelids, a subconjunctival hemorrhage in the left eye, and a swelling of the conjunctiva at the inner portion of the right eye with the conjunctiva protruding from between the lids. Examination of the abdomen revealed an apparently tender mass palpable about seven centimeters below the right costal margin. The hemogram was unchanged. A low grade temperature was recorded during the hospital stay. Ulcerated areas on the right cornea developed. The demise occurred on November 7, 1948, two months and ten days after the first hospital admission.

Dr. E. B. Vaden:

The body was that of a fairly well developed but poorly nourished white male of 2 years of age weighing 9.1 kgm. There was a brownish tint to the skin and several ecchymotic areas were present on the anterior abdominal wall and in the left antecubital fossa. The head was disproportionately large and the occipito-frontal diameter was 56.5 cm. as compared to the normal of 49 cm. for this age. There was marked proptosis of both eyeballs with ecchymosis of the periorbital tissue. The cornea of both eyes had a glazed chalky appearance. The veins of the face and forehead were very prominent. The cranial bones appeared to have been almost completely replaced by multiple, soft, raised, irregularly shaped, masses of tissue. There was separation of the bony sutures for a distance of 0.5 to 1 cm. and the anterior fontanelle was widely patent.

Upon removal of the brain extensive invasion of the calvarium by tumor forming a mat of tissue two to three times the normal thickness of the skull was observed. This mat of tissue consisted of soft, hemorrhagic, friable, gray and red tissue with scattered bony spicules. The dura was not invaded and the brain itself is not remarkable except for the compressed areas which are present and a pronounced pallor of the tissue.

In the abdominal cavity a large tumor mass, 5.0 x 3.5 x 3.0 cm., was found in the region of the right adrenal. This tumor was irregularly shaped, lobulated, and encapsulated. It pressed down upon the upper pole of the kidney, but did not involve the kidney. The cut section shows two

large lobules on of which was gray in color and fairly firm in consistency; the other was red in color, hard and contained calcium deposits. At the uppermost border of the tissue a small thin strip of adrenal tissue was seen. The left adrenal appeared normal. The liver is comparatively small, weighing 420 grams (normal 394 grams). The numerous pin-head sized areas of tumor metastases were noted over the surface. There was one marble sized area of tumor tissue in the left lobe of the liver near the round ligament. The remainder of the hepatic tissue was yellow brown in color and had the appearance of fatty metamorphosis.

Case Report No. 147

Dr. P. Kaufman C. S. 48–11805

The patient was admitted to the service by Dr. Dorothy Whipple on October 12, 1948 because of swelling of the abdomen and general poor health. The infant was born in Madagascar and known to have a protuberant abdomen at birth. For the first 3 months, the baby was kept in the hospital because she was "delicate" and needed special care. No specific medication was given. At 3 months of age the child was taken home and because the mother felt that the baby was not well she wished to come to the United States. Her physician advised against the trip. The infant progressed fairly well for a time; she smiled, laughed, held her head up and gained weight. When 5 months of age the infant's abdomen was found to be increasing in size and the blood vessels on the chest and flanks became prominent.

A month and a half later the mother first noted an ecchymosis over the baby's legs and she observed that the baby's "head seemed heavy on her shoulders."

All this time the family lived in a remote spot in Madagascar quite removed from modern medical care. On the advice of a visiting scientist the parents made arrangements to fly to Washington. In Paris the infant became acutely ill and required an oxygen tent. In New York City a diagnosis of neuroblastoma was made by Dr. R. McIntosh but at the mother's insistence the infant was brought to Washington, D. C.

The family and past history was non-contributory although the mother, a primipara, had traveled a great deal while pregnant. The gestation period was eight months without complication and spontaneous rupture of the membranes occurred two days prior to birth with a labor of 14 hours. The obstetrician had difficulty extracting the infant because of its large abdomen. The placenta is said to have weighed 960 grams. The neonatal period was apparently normal except for the large abdomen. No cyanosis, vomiting, convulsions, diarrhea, jaundice were noted. The infant gained

weight slowly but steadily and at 7 months weighed 6360 grams. Feeding consisted of a powdered milk plus vitamin D.

Physical examination on admission revealed a pale, undernourished infant lying in bed whimpering and sucking its hands. The temperature was 99.0 F. The head was held in hyperextension, it appeared large and heavy and the infant could not hold it up or move it from side to side. The anterior fontanelle was open along the saggital suture to the posterior fontanelle and measured 18 cm. by 6 cm. The fontanelle was tense and bulged slightly. The veins of the scalp were enlarged and dilated.

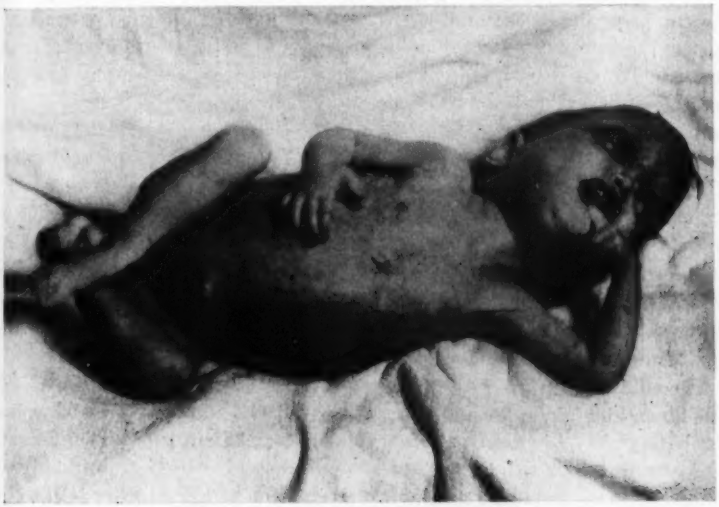

FIG. 1. Case 2. C. S. 48–11805

Examination of the eyes revealed large hemorrhagic areas visible in the lids and orbits. The eyeballs were proptosed about 4 to 5 cms. The right cornea looked normal and the pupil reacted to light. The left cornea was clouded and the pupil did not react to light. The eyegrounds could not be visualized. The ear drums and canals appeared normal (fig. 1).

There were many tumors about the head including a soft small mass on the right and left temporal regions and another in the midline over the bridge of the nose. The latter mass appeared attached to the bone but the center was fluctuant. There was a mass over the left maxilla and several along the mandible bilaterally. All the above masses were somewhat soft, non-tender, and immovably attached to the underlying structures.

The chest was small and sunken in contrast to the enlarged abdomen.

The breathing was shallow and regular with equal movements of both sides; breath sounds were normal. The heart appeared to be displaced upward. There were no murmurs or irregularity of rate. The abdomen was large and tense. A firm mass was palpable 5.5 cm. below the left costal margin; however, there was a percussible mass, without clearly defined edges, which bulged into the left flank posteriorly. The extremities were thin and had poor muscular tone. The reflexes were normal. At this time the following measurements were taken: head 46 cm., chest 36 cm., abdomen 46 cm., and length 65 cm.

The blood examination on October 14 (2 days after admission) revealed 5.5 gm. hemoglobin, 2.3 million erythrocytes and 10,200 leucocytes with 59 per cent neutrophiles, and 41 per cent lymphocytes. A urinalysis revealed the urine to be turbid, have a faint trace of acetone and many uric acid crystals and amorphous material were present.

X-ray of the extremities, chest, vertebrae were normal. Flat plate of the abdomen showed densities which were interpreted as being liver and spleen. They appeared to displace the colon and small intestine downward. Examination of the skull revealed the posterior fontanel to be closed and the anterior fontanel to be opened. There was marked tumefaction of the scalp especially in the frontal region. A destructive process involved the frontal bones and the outer table of the frontal bone showed architectural changes with strands of pericranium extending into the soft tissues. Other roentgenograms were deferred.

The infant's condition was critical throughout her hospital stay. She was given an evaporated milk formula which she took poorly. Morphine sulphate grains $\frac{1}{16}$ was given every 6 hours for evident pain. The infant's temperature began to rise on the second hospital day and gradually ascended until death on the ninth hospital day the temperature was 106.5 F.

Dr. D. Judge:

The body had a grotesque appearance but was that of a fairly well developed, moderately nourished female child. The head was irregularly enlarged with numerous bony prominences and two fluctuant masses, in the occipital-frontal circumference being 47 cm. The left maxilla and mandible were involved with similar fluctuant masses, the latter draining a cheezy yellow material into the mouth. An exopthalmos was present caused by a retro-orbital hemorrhage. The scalp veins were distended and the fontanelles were as described. No brain examination was allowed.

After opening the peritoneal cavity, a globular encapsulated mass measuring 8 x 8 cm. in the region of the right adrenal gland was easily dissected from the right kidney (fig. 2). The sectioned surface was soft and dark red, blood and several fibrous septa being noted. At the periphery an area of solid tissue having the morphology of adrenal tissue was found. The left

adrenal was enlarged and measured 1.2 x 3.0 cm. being incorporated in a tumor mass about twice its size (fig. 3). The kidneys were not remarkable.

There were numerous metastasis. The pancreas was part of a large mass (182 grams) of nodular tissue. This mass was freed from the liver and intestine but was firmly attached to the posterior peritoneal area in the region overlying the abdominal aorta. Similar masses involved the

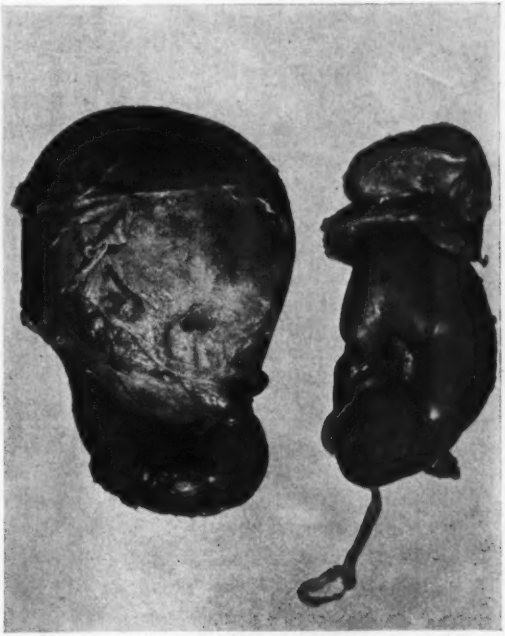

FIG. 2. Case 3. Large right adrenal tumor and kidney shown with left adrenal and kidney.

diaphragm; the nodes of the anterior and posterior cervical, supraclavicular, azygos and thoracic aorta groups. Adjacent to, but not contiguous with lumbar vertebrae L_1 and L_2 metastatic tissue was found.

The liver weighed 640 grams and contained nodules of metastatic tumor tissue which were composed of soft brown to red tissue with evidence of necrosis and hemorrhage.

Case Report No. 148

Dr. H. Kuder: N. B. 48-11771

This 2½ month old white male was admitted to the service of Dr. R. Mitchell with a chief complaint of enlargement of the abdomen.

At a routine physical examination by a physician three weeks earlier no abnormality had been noted. From that time until the time of admission the mother had noticed progressive enlargement of the abdomen with no associated complaints. There had been no anorexia, vomiting, constipation or diarrhea. The weight gain had been constant. No jaundice or bleeding had been observed.

FIG. 3. Tumor cut open showing adrenal tissue at periphery

The infant was the product of an uneventful full term pregnancy. The delivery was uncomplicated and the neo-natal course and subsequent development satisfactory. The parents and a five year old sibling were alive and well.

Physical examination on admission revealed a well nourished infant ten weeks of age, weighing 6810 grams (fig. 4). The birth weight had been 3590 grams. The physical findings of interest were confined to the abdomen which was markedly enlarged, rounded and tense. Filling the abdomen was a large smooth, nontender mass, which was apparently

entirely liver. The edges were smooth and firm, easily palpable at the level of the anterior superior spine of the iliac crest on the right and 3 cm. below the level on the umbilicus on the left. The remainder of the examination was negative. There was no lymphadenopathy.

The blood examination revealed 12,100 leucocytes with 19 per cent neutrophiles, 6 per cent eosinophiles, 72 per cent lymphocytes and 3 per

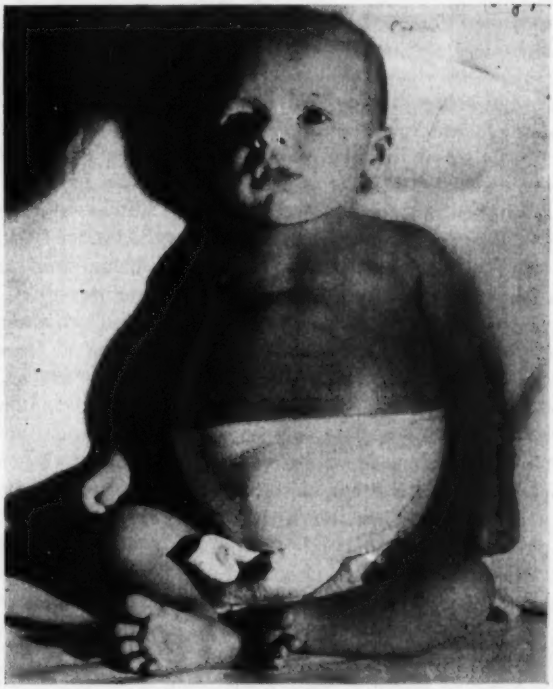

FIG. 4. Case 3. N. B. 48–11771

cent monocytes. There were 3,200,000 erythrocytes, 9 grams of hemoglobin and 200,000 platelets. The bleeding, coagulation, and prothrombin times were within normal limits. The bilirubin was 0.9 mg. per cent, the blood cholesterol 116 mg. per cent and the fasting blood sugar 91 mg. per cent. The urinalysis and Kahn were negative. A study of the tibial bone marrow revealed a slight increase in the lymphoid elements.

X-rays of the chest and the long bones of the extremities showed no abnormalities. A flat plate of the abdomen revealed a large space-occupying mass originating from the right side of the abdomen and extending

across the epigastrium to occupy the left upper quadrant. An intravenous pyelogram revealed well functioning kidneys but displacement of the calices and pelvis of the right kidney downward and medially.

A laparotomy was performed on the tenth hospital day. The liver was found to be enormous in size occupying 65 per cent of the entire peritoneal cavity. The liver appeared beefy red, nodular with interspersed areas of yellowish-grey nodules. A liver biopsy was reported as neuroblastoma, metastatic to the liver.

The infant received roentgen therapy 150 r. per day for 12 days ending November 14, 1948, when toxic manifestations developed, with no definite effect. After discharge the child did fairly well although the abdominal mass appeared to increase in size. The general nutrition was good. He was seen, as a follow-up in the Tumor Clinic on December 1, 1948 at which time it was decided that a folic acid antagonist might be given as a trial. The infant was readmitted on December 6, 1948 and examination of the abdomen at that time showed the liver to extend 13 cm. below the costal margin at the right anterior axillary liver, 12 cm. below the xiphoid and 8 cm. below the left anterior axillary line. Circumference at the costal margin was 50 cm., at the umbilicus 46 cm. He subsequently received 1 mgm. of aminopterin daily for seven consecutive days. On the second day of therapy the intermittant regurgitation of food developed into post-prandial vomiting. During the next few days the child was in an extreme state and despite all efforts fluid balance and nutrition could not be maintained. After 6 mgm. of the drug the circumference of the abdomen at the umbilicus measured 43.5 cm. as compared to 46 cm. at the beginning of therapy. On the day before death the leucocyte count and the platelet count dropped suddenly to pancytopenic levels and the drug was discontinued. Death occurred on December 13, 1948 63 days after the first admission.

Dr. D. Judge:

The body was that of a marasmic male infant weighing 5760 grams and measuring 62 cm. in length. The thoracic abdominal ratio was 2:3. The latter was enlarged and filled with a space occupying mass. A 5 cm. well healed left rectus incision was present. The skin was dry, the lips scaling. The eyes sunken. The extremities were small and showed evidence of weight loss. There was no palpable lymph nodes.

On opening the peritoneal cavity the organs were in normal relationship except for an enlarged liver which extended 8.0 cm. below the costal margin at the anterior right axillary line. A loop of small bowel, probably jejunum, was attached to the right inferior border of the liver, there being partial obstruction of this loop. The liver was hard and its surface irregular with

very little normal tissue visable. The liver was displaced by tumor masses and hemorrhagic areas. On cut section the tissue cut with difficulty and appeared fibrous. The organ was composed of a large right lobe and a smaller left with some fibrous adhesions between them. No abnormal lymph nodes were seen in the peritoneal cavity. The retroperitoneal area and kidney fossae were similarly devoid of metastatic tumor.

The left adrenal weighed 1.5 grams and was grossly normal. The right adrenal gland was replaced by an encapsulated mass of hemorrhagic tumor tissue weighing 23 grams. When sectioned it revealed soft reddish tissue and there appeared to be some compressed adrenal tissue attached to one portion of the capsule. The tumor was similar to that found in the liver.

DISCUSSION

Dr. D. Judge:

The neuroblastoma is one of the commonest tumors found in the age group from birth to five years. It was described previously as "neuroblastoma sympatheticum," "sympathicoblastoma," and "saroma of the adrenal gland." An embryonal type tumor, it is a malignant neoplasm arising from the sympathegonia, the sympathetic nervous system formative cell. These cells differentiate into sympathoblasts and sympathetic ganglion cell or the chromaffin cells of the adrenal medulla. From these various type cells arise neuroblastoma sympatheticum, the sympathogonioma, the benign ganglioneuroma and the chromaffinoma.[2] The main primary site of the neuroblastoma is the adrenal gland but it may also arise from the celiac plexes, superior cervical ganglion or other sympathetic tissue.[3, 4]

The neuroblastoma grows rapidly. At the onset it is encapsulated, but with growth, extension to surrounding organs or areas occurs. The smaller tumors are smooth but when larger they are nodular and cause confusion with the embryoma of the kidney. As seen in the cases presented here, the tumor is grayish-red in color with a vascular surface. It often can be dissected cleanly from the surrounding tissue although in older lesions it invades the surrounding tissues. On sectioning the tumor appears grayish to yellowish grey, soft, highly cellular with a supporting stroma. Often necrosis and hemorrhage occurs.

The designation of "Pepper" and "Hutchinson" types of neuroblastoma on the basis of site and metatasis seems inaccurate. The third case may represent an example of what has been described as the "Pepper" type. The latter has been used to describe cases with liver metastasis while Hutchinson first described primary adrenal tumors with metastatic spread to the skull and orbits. The microscopic pathology, of a highly cellular

neoplasm composed of small cells similar to lymphocytes with deep staining nuclei, is common to both types. The supporting stroma is scanty. Neurofibrils are seen with special staining. Mitotic figures are numerous and the presence of rosettes or pseudorosettes may aid in making a diagnosis (fig. 5).

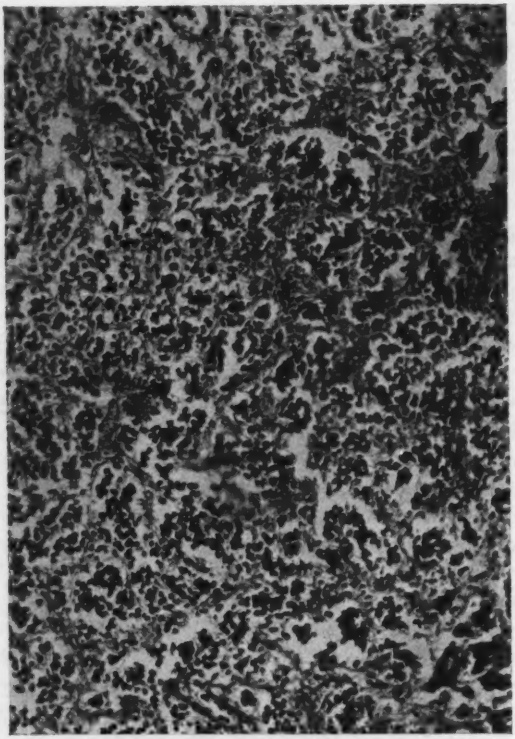

FIG. 5. Photomicrograph showing neuroblastoma of the adrenal metastatic to the liver

The early clinical picture may be limited to the accidental finding of an abdominal mass. Anemia, listlessness, anorexia, weight loss and temperature elevation may occur. As the disease progresses bone pain and lymphadenopathy are seen. Unfortunately findings of skull involvement may be the first clinical sign noted with metastasis to the orbits or auricular nodes. Occasional skin metastasis may be the first clinical evidence of the disease. Flat roentgenograms of the abdomen will reveal a mass but

along with the intravenous pyelogram may be insufficient to definitely make the diagnosis inasmuch as Wilms' and retroperitoneal tumors show similar findings. Calcification is seen most often in neuroblastoma but also can occur in Wilms' tumor. The most valuable roentgen finding for differential diagnosis is the intravenous pyelogram and the site of metastatic lesions. This unfortunately is a late manifestation of the disease. The clinical manifestations of Wilms' tumor and nuroblastoma are quite similar when the major findings are confined to the abdomen. Actually operative removal of the abdominal tumor and pathologic study offers the only definite path to diagnosis, as with all solid tumors of the abdomen in children.

Thoughts as to the method of treatment and efficacy of treatment vary. Cases have been reported in which the tumor has disappeared after a definite diagnosis was made by biopsy. This probably occurs by spontaneous hemorrhage and necrosis. Both processes are also seen often in fatal cases. Cushing and Wollach [5] first reported a case which by maturation changed to the benign gangloneuroma. We apparently have a similar case in our records. Radiation of sufficient magnitude has effected "cures" with the percentage of good results varying with certain groups. Unfortunately no standard dose of radiation is agreed upon or championed. Beneficial effects occur most readily before metastasis although even after metastasis good results have been obtained [6]. The main points for emphasis when discussing treatment are immediate adequate attention and persistent unyielding treatment despite an apparent hopeless prognosis.

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SOME PSYCHOLOGICAL AFTER-EFFECTS OF MENINGITIS*

Six Cases

Hanna Colm, Ph.D.†

This report is part of a medical and psychological study made on 320 patients following their convalescence from meningitis. A qualitative psychological study was made by me on 30 of these patients. In this article I am presenting the psychological findings on this selected group of patients. The entire group of 320 patients were studied by Doctors Vasillios Lambros, Frank Murphy and Frank Zinzi to determine if their previous meningitis had caused any neurological, developmental or physical changes. Their findings will be published elsewhere.

This group was referred to the Psychological Clinic for an intensive study because they were suspected of having been mentally affected by their meningitis. Of the thirty suspected children whom I saw, twenty-one were found to be affected mentally by the disease. The other nine, who gave the impression through lack of speech development, dependent behavior at home, or obviously poor school performance, to have been severely affected mentally, actually tested normal and even superior in the psychological study which I made of them. The inferences which could be drawn from these nine children seemed significant to me, and I should like to present some cases as illustration.

These nine children fell into two groups with different underlying dynamics behind their seeming mental or emotional impairment. The first group consisted of children with 'faked' mental symptoms. In these cases meningitis was used by an anxious and over-protective mother to protect the child from having to cope with life on a normal basis, and thus the mother actually helped the child to develop emotionally the feared mental symptom, which she had known so often to be a result of the disease. The second group consisted of children with behavior symptoms which were revealed in the psychological study as a defense against already-established emotional conflicts.

Although these symptoms were often brought on or aggravated by the meningitis, they were in reality only loosely connected with it.

The case of R. G., aged seven, represents the first group of children. She was brought to the clinic by her father, who explained that he did not know

* Grateful acknowledgment is made to Amalie Sharfman for assistance in the preparation of this article.

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too much about the child, although ever since she had had meningitis she got cross very quickly and could not learn as well in school as she had before. After her illness she began to develop quite differently from the six other children in the family, all of whom were outstanding in their school work. The doctor who had taken care of R. during her attack of meningitis had predicted that R. would probably be a little fussy afterwards, and might have some difficulty in learning.

The findings of the psychological examination were the following:

Wertham Mosaic Test: Suggested poor intellectual *functioning*—not mental deficiency. Anxiety and hostility. No organic signs.

Rorschach: No organic signs. A great deal of anxiety related to an immature acting out of 'I want what I want when I want it.' (Baby responses in content, and impulsive responses.) Intelligence normal.

Kent E. G. Y.: I. Q. low average.

In an interview with the mother, Mrs. G. told me that she had raised six other children without running into any unusual difficulties. These children behaved well and functioned normally.

True, she had a lot of work keeping seven children clean and cared for, but she seemed to feel that their health and their excellent showing in school and in the neighborhood were ample reward.

When Mrs. G. began to talk about R., two factors became evident. The remark by the doctor that R. would possibly be fussy and might have learning difficulties had caused Mrs. G. to handle R. differently from the other children; and R. was excused for her fussing and not expected to do well at school because she was 'sick.' Thus, R. was helped very little to fit into the needs and demands of the rest of the family. The feeling of the rest of the family toward R. was that of pity together with regret that Mrs. G. allowed R. to take advantage of her by using her disease as a weapon—a means of achieving power in her dealings with her mother and her father, brothers and sisters. Mrs. G.'s inability at home to help R. handle frustrations was likewise a handicap to R. in school, where again she had trouble in learning which meant in fitting into the group. Because Mrs. G. had been told to expect this type of behavior as a result of the meningitis, she did not wonder about R.'s failure in school or behavior difficulties at home, and could not be helpful in guiding her toward greater maturity.

This is obviously a case in which a healthy mother who had successfully raised six other children, became over-protective as a result of the doctor's warning about the possible after-effects of meningitis. R. took advantage of this, and produced the dreaded symptoms on an emotional basis. Often in cases of this type, the discouraging predictions of the doctor cause anxiety and over-protectiveness in an otherwise healthy mother. In R.'s case, hearsay from the neighbors and the reading of a medical book added to

Mrs. G.'s certainty that R. would inevitably be damaged by the meningitis. Because she was referred to me as one of the cases in the survey on meningitis I only saw R. for purposes of testing. Further psychological check-ups at regular intervals would have been of value, since they could have helped the mother toward a more constructive handling of R.'s problems which stemmed from emotional rather than physical causes.

The case of W. B., aged nine, belongs to the second group of children with already established emotional conflicts aggravated by the meningitis. W. had meningitis at the age of seven. In my interview with Mrs. B. she told me that W. became irritable and nervous after the attack, and did not do as well in school. Once W. had been outstanding in her school work, but now she fell into the average group. W. no longer enjoyed her piano lessons. Her father , who was an electrician, had wanted her to have these because he himself regretted so much not having been given musical and intellectual opportunities as a boy. He wanted W. and her brother to have all the cultural advantages possible. Mrs. B. reported contemptuously that the children 'naturally' minded Father better than Mother because Father used force. Asked what she meant by force, Mrs. B. replied with pent-up violence that he whipped the children sometimes, which 'broke her heart.' Mrs. B. added that she preferred to handle disciplinary problems by talking and reasoning even though she knew that she almost never got anywhere that way. She went on to tell me how tender she felt about her children—W. in particular—feeling at times that she 'feels the pain the child has to go through more than the child does.' She described a scene at the dentist where she had to leave the room because her anxiety was transmitted so strongly to W. that W. couldn't take the dentist until Mrs. B. left.

Mrs. B. had had a very strict mother, who was extremely ambitious for her daughter. Mrs. B. had consistently defied her mother's ambitions for her. She had made a very poor showing in school, while her brother, who complied with his mother's ambitions, was brilliant in his studies. W., like Mrs. B.'s brother, had been compliant until the meningitis. She and her brother had anxiously competed with each other in both their musical and school work. After the meningitis attack, however, W. as we have seen, did poorly in school and lost interest in music.

Wertham Mosaic Test: "Dynamic," design suggestive of superior intelligence.

Rorschach: Showed a very intelligent and extremely ambitious child who was caught in the conflict of: 'I want to be the best, but at the same time I long for the warmth and ease of being taken care of.' Some oppositional and defying factors were present. The two incompatible urges created a conflict in W. which caused her a great degree of anxiety.

Kent E. G. Y.: I. Q. 140.

This child's mental difficulties appeared to be exclusively emotional. In this case, the meningitis had not set off the anxiety in the mother, creating a disturbance in the mother-child relationship, but was used by the mother in an already distorted relationship to protect the child. Mrs. B. had grown up defying her own very ambitious mother by her attitude of 'I can't, I am stupid.' Moreover, she had married an overly-ambitious husband, and herself became openly overly ambitious for her children. As a result, she was caught in the conflict of being as ambitious for her children as her own mother had been, and rebelling at the same time against these ambitious feelings she projected on her children. Thus on one hand she pushed W. toward ever-greater achievement, while unconsciously also furthering W.'s defiance against being pushed. Being so closely identified with W., when W. lost out in the competition with her brother through her long absence from school through the meningitis attack, Mrs. B. compensated for W.'s not being the best in the class by blaming it on the meningitis. Soon W. herself dropped out of the competition both with her brother and at school by adopting the face-saving attitude which her mother had used. If she could not be the best she would not assert herself at all. In this case the meningitis was *used* in the dynamics of the emotional difficulties in the relationship between mother and child that obtained prior to the onset of the disease. Here again, regular psychological check-ups after W.'s meningitis would have revealed Mrs. B.'s defensive attitude and W.'s conflict which was responsible for W.'s 'mental deterioration.'

J. M., colored, eleven years, belonged to the group of children who appeared to be affected largely emotionally by the meningitis attack. I had seen her shortly before she was dismissed from the hospital, and I saw her at intervals of six months thereafter for several years. The one physical after-effect of the meningitis was the loss of the sight of one eye.

In the first examination J.'s Mosaic and Rorschach studies shortly before she was dismissed from the hospital showed organic features (organic type of perseveration), while her I. Q. tested at 71. Consecutive examinations gradually lost the organic factors, however indicated more and more stimulus-bound perseveration of the *compulsive emotional* type. (Block and stripe design in the Mosaid Test; track of a trolley car, trolley car; (also in the Rorschach several trolley car interpretations: man on the trolley car, wheel of a trolley car.) J.'s I. Q. at later testings was 129. This very delicate and extremely interesting change in the type of perseveration in the Rorschach study caused a more intensive psychiatric study of the case. The findings were as follows:

J.'s mother was left by her husband a year after J.'s birth. There were three young children in the family. J.'s father still came to see the children,

which was hard on all of them. This fact was told to me rather proudly in my interview with Mrs. M. Mrs. M. made no effort to conceal how much she hated her husband's visits. J. had always been outstanding in school both before and after the meningitis. This was of extreme importance to Mrs. M. She told me in great detail how well all three of her children did in school, and how important this was for colored children whose only chance to 'pull out' of the colored misery was through education and superior ability. Mrs. M. stated that a great deal of tension had always existed between herself and her husband because of his complete indifference to the children's education, which conflicted with her own intense ambitions for them. J.'s meningitis was especially threatening to Mrs. M. because she feared that J. might not be able to maintain her high scholastic standing as a result, and might thus lose in the fight to raise herself above the usual level of achievement of her race.

As soon as Mrs. M. had heard of the possible damage of meningitis, to the intellect, she began to help J. to become 'even better' in her studies. Mrs. M. herself had wanted to go to college, but 'wasted her chance by getting married.' She was sure that J. was the one among her children who was bright enough to go to college. Although Mrs. M. regretted that J. had lost the sight of one eye, this was insignificant so long as she kept up in her studies. As a matter of fact, Mrs. M. felt that the lost eye made it even more imperative for J. to go to college, since this impairment might make it hard for her to get a husband. Mrs. M. had brought J. to the clinic for a check up because of J.'s alarming 'nervousness' which had set in soon after J. had recovered from the meningitis. The neurological and medical findings had been negative, and J. had been referred to me in the psychological department.

J.'s compulsive and extremely anxious Rorschach and Mosaic studies, together with the lack of organic signs at that time, suggested a slowly developing emotional disturbance, with no apparent disturbance of the intellect. The onset of this disturbance was related to the threatening meningitis, but was actually only secondarily related to it. Any other threat to Mrs. M.'s neurotic ambitions would have had the same results. J. complied with her mother's ambitions and her even greater because anxiety-ridden determination that J. make a superior showing in her studies after the meningitis. This gave J. satisfaction, since it meant that she got the most out of Mother in this way, just as she had gotten it before by complying with Mother against Father's 'take it easy' philosophy.

J.'s 'nervousness' took the forms of anxiety about trolley cars. She got exceedingly restless while riding in them, and 'pestered' Mrs. M. to get out after they had ridden a short distance. J. was preoccupied with anxiety about speed. She complied intellectually to her mother's compulsive rush and speed, while emotionally she felt the need to control her mother in a

hidden and hostile way—a way that she 'could not help,' as soon as she boarded a trolley. Thus J.'s anxiety was misplaced, and seemed to pertain to the speed of the trolley cars. The trolley car symbolized at the same time the vehicle in which she was allowed to 'take it easy.' (J. showed her secret craving for being let alone in this regard in her Rorschach response where she indicated that she wanted an easy baby time.) 'I wanted to rush *and* wanted to have an easy baby time,' and a conflict developed.

The meningitis in this case had indirectly accelerated J.'s neurotic development, which was certainly present before the onset of the disease. Her symptom, fear of speeding vehicles, because of the dynamics of her relationship to her mother, and the relationship of her mother to J.'s father, was not intellectual impairment, but emotional disturbance.

The anxiety reaction about the after-effects of meningitis is sometimes found in older children, who use it as a defense and who thus rationalize about their symptoms of emotional difficulties which do not have their origin in the meningitis. E. R. was fifteen years old. He came to see me accompanied by his mother, whom I saw first. Mrs. R. told me that E. seemed all right, and that she could detect no change in him since the meningitis. He had always done well at school, although he never would do what his parents wanted him to do. He was as 'stubborn as an ass' and had been that way since he was a tiny boy. As Mrs. R. left the room she said that she was determined to fight it out with E.—after all she was the boss! It was clear that there was an exaggerated power struggle going on between E. and his mother.

E.'s Mosaic and Rorschach studies showed an intensely hostile child with a defense pattern of 'I can't help it—I am not to blame for my behavior. I hide my hostility.' His intelligence was average. At the end of the examination E. asked about the results, insisting that he suffered from after-effects of the meningitis. He explained that his memory failed him completely, not only in school, but at home as well. He fought with his parents a great deal because, as he told me, they did not make allowance for his loss of memory, which E. was sure was an after-effect of the meningitis, and which frightened him very much. Here, E.'s anxiety about his defiant, power-fighting behavior was misplaced and defensively rationalized in an evasive yet hositile pattern of: 'it's the meningitis that did this to me—I am not to blame.' E. was extremely anxious about himself and his relationship to his parents, and he was given psychiatric help in a family agency.

So far I have mentioned only those cases in which the after-effects of meningitis were brought on or aggravated by emotional causes. I should like to give briefly in two cases the effect of the mother's attitude toward growing evidence of real mental damage as a result of meningitis.

D. was the only child of Mrs. C. D. was four, but had had meningitis

when she was not quite nine months old. D. was brought by her mother, who not only felt that D. was mentally retarded, but who was worried about a slight speech defect which D. had had since learning to talk. Mrs. C. was aware of and anxious about the possibility that D. had been permanently damaged by the meningitis, and found the idea so difficult to take that she consciously tried to deny the possibility. D. clung timidly to her mother, who, to cover her fear at having to face the suspected poor result of the testing, talked constantly: "Doesn't she talk cute, Doctor? She is awfully cute and smart, Doctor. Maybe you doctor's can't see in such a short time how smart she is, but she is smart!" All during the examination Mrs. C. sat in an adjoining room with the door open, wanting desperately to persuade herself and me that her child was cute and smart.

D.'s reaction to her mother's frantic attempt to deny what she saw and actually recognized as the truth, was an anxious attempt to comply with what she knew her mother wanted from her, in spite of her inability to succeed with the test. D. fearfully followed first her mother's facial expression and response, and then my expression and response before she would commit herself to a further answer in the Mosaic study, the Rorachach, and the Binet. The result was less good than the organic mental defect would have warranted with a less anxious child. With this type of reaction both on the part of the mother and the child psychiatric help is just as important as in the cases cited above where the disturbance is largely on an emotional level. To allow such a relationship as existed between D. and her mother to go on without help can only result in a bad situation becoming worse. Although her trouble was organic, with proper guidance both D. and her mother could have been helped toward a better acceptance of D.'s condition.

The second mother whom I would like to mention in this connection had a different attitude toward her child's permanent impairment. B. was also an only child, and less than a year old when he was stricken with meningitis. He obviously did not develop quite normally, and his parents realized the situation while he was still very young. Mrs. T. brought B. to the clinic regularly for a check-up and followed with interest, warmth and full acceptance the findings made on B.'s mental development. She learned to understand his specific organic handicap, to help him deal with it, and to train him in specific ways. B.'s progress as shown by his bi-yearly psychological check-ups is steady, and unimpeded by undue anxiety on the part of his mother. The mother is enjoying the progress of her child, and she will doubtless help him to use his impaired capacities to the full.

In summarizing the results of the observations made in the research on the mental effects of meningitis, two conclusions seem warranted. In

addition to the actual mental impairment in a number of afflicted cases, there are mentally and emotionally distorted after-effects which result from the emotional attitudes of mother or child. The danger of the possible after-effects of the disease is frequently used as a weapon or a defense in the dynamics of an already-developed neurosis. A routine psychological check-up after meningitis would detect these cases where the emotional factors are predominant, and will help in the directing of these cases to psychiatric clinics where the neurotic after-effects or the neurotic use of the danger of after-effects of meningitis can be prevented or treated.

FIBROCYSTIC DISEASE OF THE PANCREAS IN EARLY INFANCY

Report of Two Cases, One Associated with Pyloric Stenosis

Fernando R. Leyva, M.D.

Fibrocystic disease of the pancreas is usually manifested in two different periods of life, each characterized by a typical but distinct clinical picture, and each perhaps determined by the degree of pancreatic achylia.

At birth, if the pancreatic achylia is sufficiently severe, it may produce an impacted meconium and consequently intestinal obstruction. On the other hand, if the degree of achylia is less pronounced, there occurs, usually after a symptom-free period of several months, digestive (steatorrhea) and nutritional disturbances with recurrent pulmonary infections. In the period intervening between these two age groups a diagnosis of fibrocystic disease of the pancreas is seldom made because the disease at that time is usually devoid of clinical symptoms. However, a small proportion of infants with this affliction in the first weeks or months of life may exhibit pulmonary or digestive findings. It is our intention to present two such patients, both of whom came to necropsy and in neither of whom the diagnosis was suspected in life.

Abram Berry, M.D. W. T. 48–5742

This six week old white male was admitted to Children's Hospital with the chief complaint of "breathing hard" and vomiting. The mother stated that the child had had spells of coughing since the age of two weeks, and "would turn blue" after each spell. The child vomited after each coughing episode and sometimes would vomit without apparent reason. Vomiting was not projectile in nature at any time. Bowel movements had been consistently normal. For two days prior to admission the child was seen by a local physician who prescribed intramuscular and oral penicillin but there was no improvement. Respirations were said to have been rapid since birth.

This infant was the product of a normal gestation and delivery. Birth weight was eight pounds. The child was bottle fed. The family history was not contributory.

Physical examination at the time of admission revealed a fairly well developed and poorly nourished six week old infant who did not appear acutely ill. The temperature was 99.2 degrees and the weight eight pounds. The remainder of the examination was essentially negative except for a slightly palpable liver.

Blood count revealed a mild anemia with 11,000 leucocytes and 53% neutrophiles with a shift to the left. X-ray of the chest revealed an area of increased density in the right upper lobe which was interpreted as being either an inflammatory process at that site or an area of atelectasis.

Following admission the child took his formula well, did not vomit and showed a weight gain of eight ounces in three days. However, on several occasions following feedings he had severe coughing spells accompanied by cyanosis which cleared quickly. A cough plate was taken and was reported negative for H. pertussis. Stools were reported to be normal throughout the hospital stay.

The infant continued to have episodes of coughing with cyanosis but in the interim showed no discomfort. On the eighth hospital day a barium "swallow" was done to rule out a "vascular ring" or any other lesion obstructing the trachea or esophagus. No compression of the trachea or esophagus was noted. An x-ray of the chest taken at the same time revealed an infiltrative lesion in the right upper lobe and marked emphysema throughout the remaining parenchyma. Following this procedure the patient began to show a gradual downhill course and soon had constant respiratory distress, cyanosis and coughing. Reexamination of the chest by x-ray showed scattered areas of atelectasis and consolidation in the right lung with emphysema at the right base and over the entire left lung. Attempts to aspirate the right upper bronchus were unsuccessful. The patient continued downhill in spite of intensive penicillin therapy, oxygen, respiratory stimulants and parenteral fluids and expired on the 14th hospital day.

Necropsy findings: The body was that of a slightly undernourished white male infant. The trachea and bronchi were filled with a pale greenish tenacious material. The lungs grossly showed consolidation of the upper lobe and emphysema of the lower lobes. Throughout both lungs mucous plugs extruded from the small bronchioles. The pancreas appeared normal grossly.

Microscopically, the lungs showed marked congestion throughout. Solid areas of bronchopneumonia and emphysema and atelectasis were present. Most of the large and terminal bronchi were moderately dilated and filled by a heavy purulent exudate. The pancreas showed destruction of acinar tissue and replacement by fibrous tissue. The ducts were dilated and many were cystic containing eosinophilic masses of material. The islets of Langerhans were fairly well preserved.

Pathologic diagnosis: Fibrocystic disease of the pancreas.

Bronchopneumonia with mild bronchiectasis.

Adrian Recinos, Jr., M.D. A. B. 47–9087

A. B., a colored male infant, was admitted to the Children's Hospital at the age of ten days because of projectile vomiting and slight jaundice of three days duration and fever beginning on the day of admission. He was delivered uneventfully at term of a primigravida and weighed 6 lbs. 14 oz. at birth. The infant was breast-fed and his appetite was excellent. He averaged two to four soft, greenish stools daily. The family history was not contributory.

Physical examination disclosed a fairly well nourished and developed,

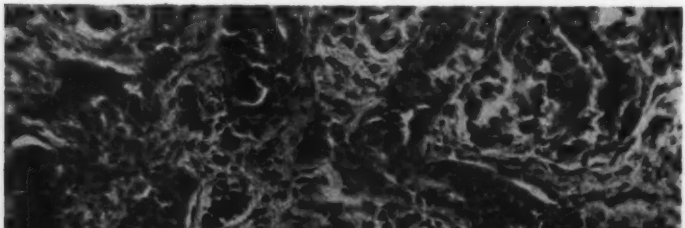

FIG. 1. A. B. Pancreas showing fibrosis, scarcity of cystic ducts and preservation of some glandular elements.

moderately dehydrated infant in no apparent discomfort. The temperature was 103 degrees and the skin dry and a pale lemon-yellow in color. A soft systolic murmur was heard over the precordium. The lungs were clear to ausculation and percussion. Waves of peristalsis were visible over the abdomen from the upper left to the lower right side of the abdomen. A walnut-sized tumor was felt in the epigastrium. The abdominal organs were not palpable.

Laboratory determinations revealed a hemoglobin of 10 grams %, erythrocyte count 3,200,000, and leucocyte count 11,000 with 64 % neutrophiles. There was mild anisocytosis of the erythrocytes and no nucleated red cells were seen. The urinalysis was normal. Determination of blood chlorides, nonprotein nitrogen, and carbon dioxide combining

power were within normal limits. The total serum protein was 5.59 grams %. The Van den Bergh showed a diphasic reaction and the bilirubin was less than 0.4 mgm. %. The patient and his mother were Rh positive.

The infant was hydrated with parenteral fluids and the temperature dropped promptly to normal. In spite of phenobarbital sedation he continued to vomit immediately after every feeding in a projectile manner. On the fifth hospital day an operation was performed and a pyloric tumor found. A pyloroplasty was performed and the infant had an uneventful post-operative course for four days.

On the fifth post-operative day the patient began to have four to six large soft stools daily but remained in fairly good condition until eleven days after operation when the stools became watery and increased in number to seven to ten daily. The infant rapidly became dehydrated and acidotic and the diarrhea remained unchecked in spite of periods of starvation and various formula changes. Several stool cultures were negative. Nevertheless, streptomycin was instituted orally. Blood transfusions and parenteral fluids were given in adequate amounts. The patient failed to respond to treatment and expired on the 16th post-operative and the 22nd hospital day.

Necropsy findings: The body was that of a markedly undernourished and dehydrated colored infant. The pylorus was enlarged and firm, the cut muscle measuring 4 mm. in thickness. The muscle had been split longitudinally for a distance of 1.2 cm. and disclosed an intact mucosa. The lumen was patent measuring 1.5 cm. in diameter. The intestinal tract was patent and the mucosa of the small intestine hyperemic and edematous. The lungs appeared atelectatic and congested. The spleen was enlarged nearly three times the normal size. The pancreas weighed 6 grams and revealed no gross abnormalities.

The abnormal histological findings were as follows: The lungs were intensely congested, the alveoli being filled with erythrocytes, serum, and pigment deposits. In a few areas mononuclear cells had infiltrated the alveolar and bronchial walls. There was an increase of fibrous tissue in the pancreas. Many glandular acini were replaced and others distorted by this abundant fibrous tissue. The islets of Langerhans appeared normal and stood out prominently from the fibrous background. The salivary glands were not studied histologically because the diagnosis of fibrocystic disease was suspected neither in life nor at necropsy. Sections through the pylorus revealed a marked thickening of both circular and longitudinal muscle fibers. The liver showed moderate periportal infiltration by mononuclear cells and lymphocytes. The sinusoids were moderately congested and distended by erythrocytes. The hepatic cells appeared normal. The splenic pulp was moderately congested.

Pathologic diagnosis: Subacute enteritis; fibrocystic disease of the pan-

creas; hepatitis, mild; pulmonary congestion and atelectasis; post-operative pyloroplasty.

DISCUSSION

Fernando R. Leyva, M.D.

The two patients presented bring up several interesting points for discussion. W. T. illustrates one of the most unusual manifestations of fibrocystic disease; mainly, an extremely early onset (two weeks of age) of pulmonary infection with, however, no digestive symptoms. A. B., on the other hand, exhibited no signs or symptoms of fibrocystic disease but succumbed to an intractable watery diarrhea following a pyloroplasty. The coexistence of pyloric stenosis and fibrocystic disease of the pancreas in this patient is noteworthy because of the rarity of this combination.

Why cases with apparently similar morphological changes in the pancreas and presumably a similar degree of pancreatic insufficiency should have different clinical manifestations is difficult to determine. The deciding factor may well be the *degree* of pancreatic achylia. If this is so, one might suspect that the degree of destruction of pancreatic tissue is proportional to the degree of achylia. In other words, a patient with *early* severe clinical manifestations should have a marked achylia and advanced destructive changes in the pancreas while another of the same age with mild symptoms should have a minimal achylia and less advanced changes in the pancreas. A careful examination and comparison of the pancreatic tissues in our cases give support to this hypothesis.

Histologically, A. B., (Fig. 1.) who had no clinical manifestations of fibrocystic disease, shows less involvement of the pancreas than W. T. There is less proliferation of fibrous tissue and fewer cystic ducts. In some areas the glandular elements are fairly well preserved. Sections from W. T., (Fig. 2.) the patient with marked pulmonary disease, on the other hand, exhibit the more typical picture of advanced fibrocystic disease. The pancreatic ducts are dilated and distorted and many are cystic or atrophic. The acinar tissue is atrophic or replaced by fibrous tissue. It is unfortunate that determinations for pancreatic enzymes were not made in these patients.

Very little is known of the pathogenesis of the pulmonary changes in fibrocystic disease. This is unfortunate because the degree of pulmonary pathology largely determines the ultimate prognosis.

It has been suggested recently that the lesions of fibrocystic disease of the pancreas are essentially similar in etiology, if not in morphology, to those of polycystic disease of the kidney, liver, lung etc. The rarity of extensive polycystic lesions of the pancreas in adults is explained by their early death, as children, with fibrocystic disease of the pancreas.

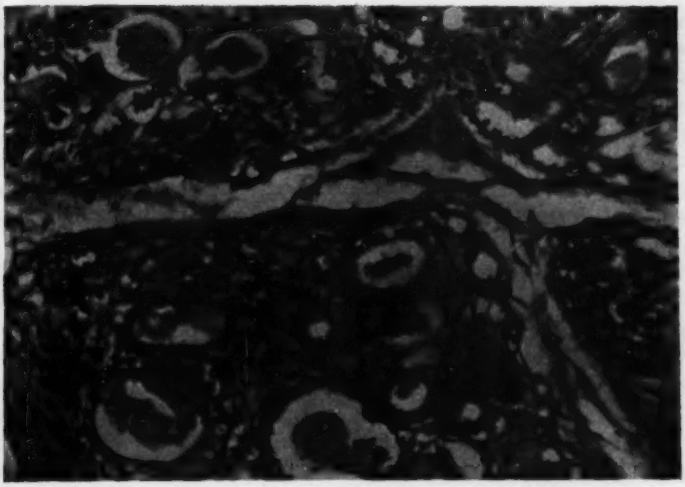

FIG. 2. W. T. Pancreas showing more advanced cystic changes, retention of secretions and destruction of parenchyma, than A. B.

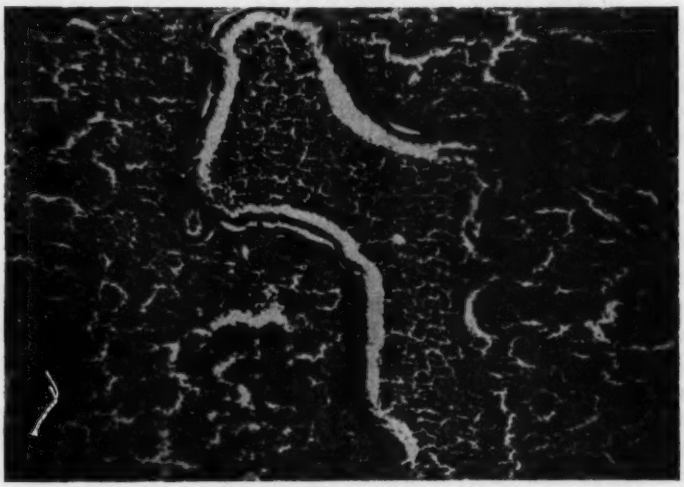

FIG. 3. W. T. Lung and Bronchus. Extensive Bronchopneumonia

Another interesting question is whether the changes in the pancreas are present at birth or appear later in life. The congenital origin of fibrocystic disease has been questioned particularly in cases with onset of clinical

symptoms after a symptom-free period of several months. The two cases reported here suggest that the anatomical changes in the pancreas are present at birth or occur very early in life. In particular, A. B., who may be called an "asymptomatic" case of fibrocystic disease and yet had considerable pancreatic fibrosis at 32 days of age, lends strong support to the congenital etiology of this disease. It might be assumed that had this patient survived, he would have been symptom free for weeks or months and then developed digestive, nutritional and pulmonary symptoms.

The exact mechanism responsible for the changes in the pancreas and the other organs has not been definitely established. Infections, heredity, congenital malformations of the pancreatic ducts and dietary deficiencies have been suggested. Most authorities, however, believe that an abnormal exocrine secretion of the pancreas and perhaps other organs is the basic abnormality. This opinion can best be expressed by quoting from Andersen: "Cystic fibrosis of the pancreas represents the commonest manifestation of a hereditary disease which may also involve the intestinal glands, the intrahepatic bile ducts, the gall bladder, and occasionally other epithelial glands, and which has as its primary feature the production of abnormal secretion of these glands, the morphologic features being secondary."

There is little to say about the occurrence of pyloric stenosis in one of our patients (A. B.). The coexistence of fibrocystic disease of the pancreas and pyloric stenosis in the same patient has not, to our knowledge, been previously reported. In all probabilities they are incidental findings with no other significance.

DISCUSSION

Hugh Davis, M.D.

Our knowledge of cystic fibrosis of the pancreas dates back to 1905 when Landsteiner made the first pathologic description of the pancreatic lesion. However, it was only in 1938 that the clinical syndrome was first recognized by Andersen. Since that time many case studies have appeared in the literature and this disease has been noted with increasing frequency. At first the diagnosis was made primarily at the autopsy table. However, since 1938 when increased emphasis was placed on this disease entity by Andersen and others, the diagnosis has come to be made frequencly antemortem.

The disease is considered to be congenital and familial in character but the etiology is still unknown. Its onset in infancy is characterized by failure to gain weight in spite of adequate food intake and the presence of severe cough with excessive mucus in the respiratory tract and a tendency to recurrent respiratory infections. Large, foul smelling stools and

wasting of the buttocks and extremities are fairly common findings in children who survive very long. When suspected, the diagnosis is usually confirmed by the absence of pancreatic ferments, especially trypsin, from the duodenal juices. Andersen has stated in a recent paper that analysis of duodenal contents is hardly necessary for diagnosis. The characteristic signs and symptoms found in the respiratory tract with failure to gain in spite of an adequate caloric intake are usually sufficient to make one strongly suspect cystic fibrosis of the pancreas, in fact almost be sure of the diagnosis.

In a report of her recent investigations, Andersen now stresses the bronchial lesion advancing the hypothesis that the latter, like the pathology of the pancreas, is congenital. In her opinion there may be something wrong with the cilia of the bronchi causing the large accumulation of thick tenacious mucus which cannot be differentiated from that of pertussis or asthma.

When infection occurs, it is usually staphylococcal at first; later a mixed infection with pyocyaneus is common. Andersen points out that while these babies have bronchopneumonia early they are never born with it, that is, there is a congenital respiratory lesion but no infection. Infection, which of course is the serious factor in these cases, comes later.

The prognosis has improved somewhat with early diagnosis and proper therapy. However, the oldest case on record at this time is 14 years. The treatment consists mainly of (1) proper dietary regime to provide for adequate nutrition, (2) avoidance of infection, (3) high vitamin A content, (4) use of pancreatic granules and (5) proper therapy for the respiratory involvement. Andersen recently has become doubtful of the value of vitamin A. Although there is a deficiency of this vitamin, administration will not help. The most important part of treatment is avoidance of infection. The diet may be general. Those cases that survive do well on a selective diet.

These cases of cystic fibrosis of the pancreas are being presented as two of the youngest seen at Children's Hospital. In the second patient, W. T., the stools were reported as normal. This would be expected at the early age of this patient. Sufficient findings were present to suggest the diagnosis if it had been kept in mind. The main emphasis in this case was placed on the pulmonary findings and these should have given the clue to the diagnosis. Since the prognosis has been improved by early diagnosis and treatment, one must re-emphasize the importance of including cystic fibrosis of the pancreas in the differential diagnosis of any infant who gives a history of failure to gain weight and of respiratory signs and symptoms with large amounts of thick tenacious mucus. Even before infection of the respiratory tract occurs in a young patient such as the one reported here the diagnosis is obvious.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: D. Joseph Judge, M.D.
Edwin Vaden, M.D.
By Invitation: Lewis K. Sweet, M.D.

D. Joseph Judge, M.D.

This five year old white male was admitted to the hospital because of headache, lassitude, weakness for 24 hours and the onset of vomiting 12 hours previously.

Six weeks prior to admission the child was hit on the side of the head by a swing but apparently suffered no ill effect. He had been well and had a tonsillectomy and adenoidectomy at the Episcopal Hospital. Ten days post-operatively he ran a temperature of 99 to 102 degrees F. The throat seemed to heal rapidly. Five days prior to admission he again developed fever. Examination of his blood at that time revealed 13,500 leucocytes with 68 per cent polymorphonuclear leucocytes. The urine examination was negative. He received 100,000 units of penicillin orally every four hours for one and one half days without change of the temperature, then sulfidiazine was given for 3 to 4 days. On the day of admission the child seemed more prostrated, slight neck rigidity was also present. The knee jerks were normal and no paralysis was present. He had always been unable to wink with his right eye. The leucocyte count was 17,300 with 72 per cent polymorphonuclear present. Agglutination tests for typhoid and paratyphoid, undulant and Rocky Mountain Spotted fevers were negative. He was admitted to the hospital because there was no improvement under the chemotherapy prescribed by the private physician and because of the development of neck rigidity and vomiting.

The past history includes normal labor and delivery, breast feeding, the usual immunizations and occasional attacks of tonsillitis of moderate severity for which a sulfa preparation was given. The family history is non-contributory.

On admission to the hospital the child was drowsy, had a temperature of 102 degrees F. and appeared acutely ill. There were enlarged cervical lymph nodes, 2 plus nuchal rigidity and a suggestively positive Babinski on the right. The pharynx was slightly injected and throat culture revealed hemolytic streptococcus. A spinal fluid examination the night of admission revealed 50 leucocytes per 100 mm^3., 60 mgm. per cent protein and 40–50 mgm. per cent sugar, 65 per cent of the cells being lymphocytes. The following day the cells numbered 400, with 51 per cent polymorphonuclears, 40 mgm. per cent protein and 45 mgm. per cent sugar. No or-

ganisms were found on direct smear or on culture of the spinal fluid. The child showed weakness of the upper and lower extremities, increased drowsiness, a right facial paralysis and absent knee jerks. At this time the right pupil was found to be smaller than the left and both reacted sluggishly to light.

On the third hospital day the coma seemed deeper. The temperature rose to 102 degrees F. and generalized muscular twitchings occurred. At 11:00 A.M. a lumbar tap was done and between 25 and 30 cc. of cloudy fluid was obtained under considerably increased pressure. The protein was 200 mgm. per cent with 40 mgm. per cent of sugar. At 1:00 P.M. the temperature was 104 degrees F. and light convulsive movements were reported by the nurse. At 4:00 P.M. the nurse's notes stated that the breathing was rapid and deep and seemed to be on the left side only. A half hour later the respirations were shallow, the patient suddenly became cyanotic and ceased breathing. Artificial respiration and stimulants revived the patient at this time. The temperature had risen to 106 degrees F. He was placed in a respirator and mucus aspirated from the throat. At 5:15 P.M. another cyanotic attack occurred and he was pronounced dead at 5:30 P.M. The blood leucocyte counts in the hospital were 12,000 and 22,000.

Dr. L. K. Sweet:

In discussing this patient's condition I would like to assume a somewhat chronological approach, and begin by considering the various diagnostic possibilities that seem to be pertinent at the time of admission. I will then follow them with a discussion of the effect of the various developments noted on the presumptive diagnoses.

To begin with, we have a five year old boy who sustained an injury to his head six weeks before entry. He then had a tonsillectomy ten days before entry. He had had a fever continuously from the time of operation until his hospital admission. The fever had persisted despite penicillin and sulfadiazine, and he had developed prostration and evidences of meningeal irritation. On admission he presented a streptococcus pharyngitis, a moderate leucocytosis, and a spinal fluid that contained fifty cells, sixty-five per cent lymphocytes, a slightly increased protein and a normal sugar. What are the diagnostic possibilities?

In my thinking, the first important differentiation to be made in a patient with meningitis is as to whether the inflammatory process is serous or purulent in nature. In serous types of meningitis, the predominant type cell found is a mononuclear leucocyte, while in purulent types of meningitis the predominant cell is a pus cell, or a polymorphonuclear leucocyte. It is true that one cannot always be sure from a single

examination that the cell type will be stable and will not change. In poliomyelitis, for example, it is fairly common to find pus cells present in the spinal fluid early in the disease, with lymphocytes later. Also, in meningitis due to *H. influenzae*, and in some other types of purulent meningitis, one occasionally sees a lymphocytic response early in the disease, with a shift to polys later on. With regard to the patient under consideration, if we put ourselves in the position of the physician who saw this child on admission, we will have to think first and foremost of some type of serous meningitis as being the cause of his illness.

The following outline gives the various etiologic agents that cause a serous meningitis:

I. Virus infections of the Central Nervous System
  1. Primary infections:
    A. Rabies
    B. Encephalitis
      (1) St. Louis, Japanese B, Australian X.
      (2) Equine, Eastern and Western
      (3) Von Economo's encephalitis
      (4) Other forms, as Russian Spring and Summer, Louping-ill, etc.
    C. Poliomyelitis
    D. Lymphocytic choriomeningitis
    E. Other rare forms of virus meningitis, e.g. herpes simplex.
  2. Secondary infections:
    A. Meningoencephalitis secondary to
      1. Vaccinia
      2. Measles
      3. Mumps
      4. Chicken pox
      5. Rubella
    B. Meningoencephalitis in other infections
      1. Lympho-granuloma venereum
      2. Infectious mononucleosis
  3. Secondary infections of probable virus etiology
    A. Serious meningitis and encephalitis complicating scarlet fever
II. Bacterial infections
  1. Tuberculosis
III. Spirochetal infections
  1. Syphilis
  2. Weil's disease
IV. Chemical inflammation
  1. Lead encephalitis

V. Fungus infections
   1. Torula meningitis
VI. Protozoan infections
   1. Toxoplasmosis
VII. Irritative inflammation.
   1. Brain abscess
   2. Brain tumor

As we proceed down this list of diseases, there is nothing in the history or physical examination to make us think of rabies. Encephalitis is so protean in its manifestations that a diagnosis can be neither made nor excluded. The fever, leucocytosis and drowsiness lead us to hold this condition as a diagnostic possibility. Since a specific virus etiology can be established only during an epidemic, or after long time virus study, it is futile to speculate on a specific virus, save to mention that equine encephalomyelitis or St. Louis encephalitis are the primary virus encephalitides that might be encountered in this locality.

Poliomyelitis cannot be excluded in this patient, and must be considered a very likely diagnostic possibility. The drowsiness is uncommon, and the leucocytosis is somewhat higher than is usually encountered. However, the remainder of the initial findings are sufficient to cause considerable likelihood of this being the correct diagnosis. The lack of bulbar symptoms in a patient who had a recent tonsillectomy may be an additional point against polio. Lymphocytic choriomeningitis and other primary virus types of meningitis seem to me to be entirely unlikely. In our experience, the spinal fluid cell count has been higher, and we have encountered no instances of these infections where the differential cell count showed less than ninety per cent lymphocytes. The secondary virus infections can be excluded *en mass* for want of an antecedent infection, no history of exposure, and no other evidence of a primary systemic disease. Mumps is the only one of these conditions that cannot be excluded entirely on these grounds. However, the whole picture fails to suggest mumps to me.

Among the non-viral conditions, tuberculosis is a good possibility. As a rule the spinal fluid protein is higher, the dextrose lower. However, these findings may be more prominent later on; their absence is not conclusive. We have also, the drowsiness and suggestive peripheral neurological findings (the Babinski on the right) which are compatible with tuberculosis. Studies to prove or exclude the diagnosis of systemic tuberculosis are needed to shed more light on the probability of this diagnosis.

Spirochetal infections are not likely. Syphilis is an unusual cause of meningitis in a boy of this age. Furthermore, in my experience, syphilitic meningitis rarely causes as much fever and systemic illness as is encountered

here. Weil's disease could cause a picture like this, though jaundice should be evident if such were the case. Lead encephalitis can be excluded only by a finding of normal long bones by x-ray (without lead deposits) and normal red blood cells, without stippling. I see no reason to consider fungus or protozoal infections of the central nervous system.

That leaves only a space occupying lesion in the brain. If this were a brain abscess, it would seem, from the initial spinal fluid finding, that it must be a chronic or sub-acute process since the spinal fluid cellular response is lymphocytic. An acute brain abscess, such as suggested by the history, is much more likely to be associated with a purulent reaction in the spinal fluid. Therefore, at the time of admission, a brain abscess would seem to be very unlikely. The same would be true of a brain tumor which should not cause so much fever and other evidence of acute illness.

From this review, then, it would seem that the most likely diagnosis at the time of admission would be an acute encephalitis, poliomyelitis, and tuberculous meningitis. Now let us turn to the patient's hospital course and see what further light can be shed on the subject.

The day after admission the spinal fluid showed 400 cells, fifty-one per cent polys. This finding seems almost sufficient to exclude a diagnosis of poliomyelitis as the shift from lymphocytes to polys is in the wrong direction for this disease. However, the patient developed paralyses, increased drowsiness, and pupillary signs. The increasing drowsiness and pupillary inequality also militate against polio. The peripheral paralysis would seem to exclude, or at least argue against, encephalitis. While it is unusual to find as many as fifty per cent polys in tuberculous meningitis, and while the low protein in the spinal fluid also is extremely unusual, it would seem that tuberculosis would hold a diagnostic advantage at this point. However, none of our primary diagnoses are on a firm footing now, and other possibilities should be kept in mind.

The finding, on the third day, of a purulent spinal fluid, along with the advent of coma and convulsions, definitely rules out all our first impressions, and makes us shift our thinking from a serous to a purulent meningitis. And here we are struck by the normal spinal fluid dextrose and the repeatedly negative reports for bacteria by smear and culture on the previous spinal fluids. The one condition that could cause such a state of affairs would be a brain abscess. Any other type of purulent meningitis should have yielded a positive culture before this time, and the dextrose content of the spinal fluid should have been diminished markedly. A brain abscess, or an extradural abscess, can and often does cause a purulent meningitis which is sterile on culture and causes no reduction of the dextrose content of the spinal fluid.

But why should a boy of five suddenly develop a brain abscess? Here

the history is of extreme importance. Six weeks previously the boy had been hit on the head. We have no knowledge of the seriousness of the accident, and it may have been completely innocuous. However, it may have caused a contusion of sufficient importance in the brain to create a focus of lowered resistence. Then, some four weeks later the tonsils and adenoids were removed. This may have initiated a transient bacteremia which resulted in a localization at the site of the previous contusion, with abscess formation. But do we have evidence that tonsillectomy will cause a bacteremia, however transient? I think we do. I have seen several patients with remote bacterial infections, caused by the same organism as that cultured from the tonsils, occurring one to two weeks after tonsillectomy. And there is experimental support for this hypothesis in work done recently at the Gallinger Hospital by Doctors Hirsh, Vivino, Dowling and Merril.[1] They have taken blood cultures immediately after dental extractions and later after intervals of approximately ten and thirty minutes. The blood was cultured both aerobically and anaerobically. In control patients the incidence of cultures positive for non-hemolytic streptococci was thirty-five per cent, whereas in patients previously treated with penicillin, the incidence of positive cultures for streptococci was reduced to seventeen per cent. Interestingly enough, the incidence of positive cultures did not increase with the amount of pyorrhea and infection in the mouth. It did increase, however, when extensive surgery was required to effect the extraction. These findings, it seems to me, offer a possible explanation as to why the boy suddenly developed a brain abscess.

One final point: We have yet to localize the abscess that we think to be present. My knowledge of neurological anatomy is not too exact, but I would guess that the abscess would be on the left side, probably involving the internal capsule.

PATHOLOGIC DISCUSSION

E. Clarence Rice, M.D.

The body was that of a white male having an apparent age of five years. The lips were cyanotic and dark brown fluid poured from the nose. Cloudy cisternal fluid was obtained by puncture.

Of greatest significance was the examination of the skull and brain. The mastoid air cells were normal and the vascular and nasal accessory sinus revealed no abnormalities. The brain weighed 1560 grams, the normal being 1237 grams. It filled the cranial vault completely. The left cerebral hemisphere seemed larger than the right and had a fluctuant consistency. The cortical convolutions were generally flattened. There was no exudate involving the meninges. When the wall of the left lateral

ventricle was incised approximately 15 cc. of bloody malodorous pus escaped. Section revealed the tissue to be edematous. A horizontal section revealed an abscess of the left frontal lobe which measured 3.4 x 2.5 x 7.5 cm. and involved the internal capsule anteriorly, the basal ganglia and posteriorly the thalamus. There was no definite capsule. The left lateral ventricle was compressed by the abscess, the right somewhat dilated. Coronal section indicated that the abscess had ruptured into the left lateral ventricle. The spinal cord was normal.

An interesting finding sometimes associated with brain lesions was noted in this patient was the finding of approximately 150 cc. of dark brown fluid associated with some fatty material in the left pleural cavity. A 6 cm. opening through the parietal pleura for a distance of 3 cm. at the angle of the ribs exposed the posterior mediastinum. The visceral pleura was absent over the lung surface for a distance of 1.5 cm. from the hilus leaving a jagged bleeding area. The reparation of the pleura extended down to the esophageal hiatus. A perforation of the esophagus and erosion of the infereior hemiazogos vein at the point where the left crosses from left to right to join the azygos vein was found. The right pleural cavity contained approximately 20 cc. of the same brown fatty material as noted on the opposite side. A small perforation of the parietal pleura 2 cm. in length at the level of the ninth rib allowed communication between the two pleural cavities through the posterior mediastinum. The right lower lung was airless, purple in color and of rubbery consistency. A number of hemorrhagic areas varying in size from 0.5 to 1.0 cm. in diameter were present. The left lower lobes had some small pleural collections of blood and the cut surface showed hemorrhagic areas, apparently infarcts.

Examination of the gastro-intestinal tract revealed the erosion of the esophagus and the cardiac end of the stomach on its greater curvature. Some stomach contents were present between the stomach and spleen. The stomach contained a large amount of mucus. No evidence of hemorrhage is found in the intestinal tract. The examination of the other organs gave no pertinent information.

Bacteriological Examinations:

Pus from brain abscess—Culture non-hemolytic streptococcus.

Cisternal fluid—Smear—no bacteria seen. Culture—no growth.

Heart's blood—contaminated.

Microscopic examination of the brain showed a typical abscess with practically no walling off by connective tissue. The adjacent areas shows hemmorrhage, thrombosis of blood vessels and degeneration of brain tissue. Extending outward, proliferation of blood vessels, perivascular leucocytic infiltration, occasional perivascular fibrosis and some perivascular hemorrhage is observed. An increased number of astrocytes is found. Some

infiltration of mononuclear cells in the subarachnoid space is evident. The lungs show areas of pulmonary infarction. Fatty metamorphosis of the liver is present. The spleen and liver are congested.

Pathologic diagnosis: Brain abscess, left cerebral hemisphere. Erosion of esophagus, stomach and inferior hemiazgos vein with hemothorax and extension of stomach contents.

Pulmonary infarction.

Fatty metamorphosis of the liver.

It is interesting that this is the second patient to come to necropsy recently with a cerebral abscess following a tonsillectomy. This is not a common finding following this procedure and to my knowledge represents the only complication of this sort in several thousand tonsillectomies at this hospital. The fact that it can happen suggests the advisability of preoperative and postoperative chemo- or antibiotic therapy.

REFERENCE

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